The N-end rule pathway is a sensor of heme.

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Public Summary:

Scientific Abstract:
The conjugation of arginine, by arginyl-transferase, to N-terminal aspartate, glutamate or oxidized cysteine is a part of the N-end rule pathway of protein degradation. We report that arginyl-transferase of either the mouse or the yeast Saccharomyces cerevisiae is inhibited by hemin (Fe(3+)-heme). Furthermore, we show that hemin inhibits arginyl-transferase through a redox mechanism that involves the formation of disulfide between the enzyme's Cys-71 and Cys-72 residues. Remarkably, hemin also induces the proteasome-dependent degradation of arginyl-transferase in vivo, thus acting as both a "stoichiometric" and "catalytic" down-regulator of the N-end rule pathway. In addition, hemin was found to interact with the yeast and mouse E3 ubiquitin ligases of the N-end rule pathway. One of substrate-binding sites of the yeast N-end rule's ubiquitin ligase UBR1 targets CUP9, a transcriptional repressor. This site of UBR1 is autoinhibited but can be allosterically activated by peptides that bear destabilizing N-terminal residues and interact with two other substrate-binding sites of UBR1. We show that hemin does not directly occlude the substrate-binding sites of UBR1 but blocks the activation of its CUP9-binding site by dipeptides. The N-end rule pathway, a known sensor of short peptides, nitric oxide, and oxygen, is now a sensor of heme as well. One function of the N-end rule pathway may be to coordinate the activities of small effectors, both reacting to and controlling the redox dynamics of heme, oxygen, nitric oxide, thiols, and other compounds, in part through conditional degradation of specific transcription factors and G protein regulators.

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